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Clinical Efficacy of Combined Use of Azilsartan with Indapamide and Azilsartan with Nitrendipine in Patients with Arterial Hypertension

Z. T. Mashkurova, G. Zh. Abdullaeva*, G. A. Khamidullaeva, N. Kh. Sherbadalova, M. N. Khatamova, Zh. B. Safarov, M. I. Atoeva

Republican Specialized Center of Cardiology
Tashkent, Uzbekistan

Abstract

The aim of our study was a comparative evaluation of the effectiveness of the combined use of azilsartan with indapamide, and azilsartan with nitrendipine in achieving antihypertensive and organ-protective effects in patients with arterial hypertension (AH).

Methods and Results: The study included 101 patients aged 30-75 years (mean age of 53.1±11.2 years) with AH Grades 1-2 (ESC/ESH, 2018), who were on outpatient treatment at the Republican Specialized Center of Cardiology (Tashkent, Uzbekistan).

After the screening stage, all patients were discontinued from previous therapy and assigned to the 2 regimes of dual therapy. Group 1 included 50 AH patients treated with azilsartan (Az) and indapamide (Ind); Group 2 included 51 patients treated with Az and nitrendipine (Nit). The average daily dose of Az was 49.3±6.0 mg, Nit - 10.88±4.3 mg, and Ind - 1.69±0.5 mg. The effectiveness of the prescribed therapy was evaluated after 6 months of treatment.

The 6-month dual therapy with Az+Ind and Az+Nit is characterized by high antihypertensive efficacy with a significant positive effect on the parameters of diurnal blood pressure (BP) profile in AH patients. Achieving the target level of BP in both groups provided high organ-protective efficacy, expressed in a significant regression of LV hypertrophy and LV dimensions, a decrease in the carotid intima-media thickness (CIMT) and arterial rigidity. However, the best cardio- and vaso-protective efficacy was noted in Group 1, which was expressed in a more pronounced improvement in the left ventricular diastolic function, a decrease in the CIMT on both sides, and a significant improvement in the parameters of central hemodynamics and arterial stiffness. Dual therapy with Az+Ind and Az+Nit in AH patients was accompanied by a positive effect on the metabolic profile and excellent nephroprotection, with an advantage in the Az+Ind group. A significant decrease in the blood level of low-density lipoprotein cholesterol, total cholesterol, and uric acid is characteristic in both groups of patients. A significant decrease in the levels of fasting blood glucose and triglycerides occurs only in the Az+Ind therapy.(**International Journal of Biomedicine. 2022;12(3):367-374.**).

Keywords: arterial hypertension • arterial stiffness • left ventricular hypertrophy • antihypertensive medication

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Abbreviations

AH, arterial hypertension; **AS**, arterial stiffness; **AHM**, antihypertensive medication; **ACEIs**, angiotensin-converting enzyme inhibitors; **ARBs**, angiotensin receptor blockers; **AIx**, augmentation index; **BP**, blood pressure; **CCA**, common carotid artery; **CCBs**, calcium channel blockers; **DBP**, diastolic BP; **DBPP**, diurnal blood pressure profile; **FBG**, fasting blood glucose; **GFR**, glomerular filtration rate; **HDL-C**, high-density lipoprotein cholesterol; **CIMT**, carotid intima-media thickness; **IVST**, interventricular septal thickness; **LVMI**, left ventricular mass index; **LVDF**, left ventricular diastolic function; **LVH**, left ventricular hypertrophy; **LVEDV**, left ventricular end-diastolic volume; **LAV**, left atrial volume; **LAVI**, LAV index; **LDL-C**, low-density lipoprotein cholesterol; **PP**, pulse pressure; **PWV**, pulse wave velocity; **LVESD**, left ventricular end-systolic dimension; **LVEDD**, left ventricular end-diastolic systolic dimension; **PWT**, posterior wall thickness; **SBP**, systolic BP; **TC**, total cholesterol; **TG**, triglycerides.

Introduction

Arterial hypertension (AH) remains a major risk factor for cardiovascular complications and death.[1] AH is diagnosed in a third of the world's population and annually leads to the death of almost 10 million people (ESC/ESH, 2018).

Large epidemiological and clinical studies have shown that high blood pressure (BP) plays a significant role in the development of a dramatic increase in the risk of cardiovascular events, including fatal ones. In particular, the risk of cardiovascular events, including coronary heart disease, cerebrovascular disease, and kidney damage, is directly related to the SBP level.[2]

According to current recommendations, the approach to the treatment of AH has changed significantly, based on evidence-based medicine, taking into account the pathogenesis of the disease. Despite significant progress, however, a number of problems associated with complications and therapy of this disease remain unresolved. One of the main problems of AH is damage to organs and systems, including the pathogenesis of left ventricular hypertrophy (LVH), endothelial dysfunction, and kidney damage.

According to a number of studies, arterial stiffness and endothelial dysfunction, which are closely associated with vascular remodeling during aging, in hypertension, chronic renal failure, diabetes mellitus, and other conditions, are independent risk factors for cardiovascular mortality and general mortality in patients with atherosclerosis.[3] The Consensus Document of the European Experts on the use of arterial stiffness (AS) in the diagnostic and therapeutic process (2006) states that the determination of AS has an advantage over classical risk factors, as it directly reflects the actual damage to the vascular wall. According to some studies, at the same level of BP in patients with hypertension, the pulse wave velocity (PWV) is most often increased in contrast to intima-media thickness (IMT) or left ventricular mass index (LVMI).[4,5]

Based on current European Guidelines (ESC/ESH, 2018),[1] most patients are indicated to start therapy with a dual combination of drugs: angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) + diuretic or calcium channel blocker (CCB). The exception is patients with low BP (close to normal BP values), very elderly, and debilitated people. A relatively new member of the ARB class is azilsartan, which has a high affinity and reliable binding to AT1 receptors, which provides a powerful and long-lasting antihypertensive effect, convincingly demonstrated in previous studies.[6-10] In particular, according to the office measurement of BP and daily monitoring, azilsartan showed statistically significant superiority in reducing BP, compared with valsartan, candesartan, and olmesartan.[11] It is well known that the most commonly prescribed and most studied dihydropyridine CCB is amlodipine. The high antihypertensive and organ-protective efficacy of amlodipine have long been known. At the same time, CCB nitrendipine, which exhibits neuroprotective activity, is also of interest. Thiazide and thiazide-like diuretics remain the gold standard for any combination therapy. One of the brightest representatives of this group of diuretics is indapamide, a distinctive feature of which is its metabolic neutrality and vasodilatory activity. The pronounced positive effects of indapamide in elderly patients and patients with heart failure make it a priority in most patients with AH.

The aim of our study was a comparative evaluation of the effectiveness of the combined use of azilsartan with indapamide, and azilsartan with nitrendipine in achieving antihypertensive and organ-protective effects in AH patients.

Materials and Methods

The study included 101 patients aged 30-75 years with AH Grades 1-2 (ESC/ESH, 2018), who were on outpatient treatment at the Republican Specialized Scientific and Practical Medical Center for Cardiology. Exclusion criteria were symptomatic hypertension, valvular heart disease, acute coronary syndrome, chronic heart failure (NYHA FC>III), cardiac arrhythmia, history of stroke and myocardial infarction, diabetes, occlusive peripheral arterial disease, renal impairment, severe co-morbidities, orthostatic hypotension.

After the screening stage, all patients were discontinued from previous therapy and assigned to the 2 regimes of dual therapy. Group 1 included 50 AH patients treated with azilsartan (Az) and indapamide (Ind); Group 2 included 51 patients treated with Az and nitrendipine (Nit). The average daily dose of Az was 49.3±6.0 mg, Nit - 10.88±4.3 mg, and Ind - 1.69±0.5 mg. The effectiveness of the prescribed therapy was evaluated after 6 months of treatment. Dosing of AHM, taking into account the maximum doses, was titrated at 2-week intervals to achieve a target blood pressure.

The effectiveness of therapy was assessed by achieving the target BP level according to 2018 ESH/ESH Guidelines for the management of AH. The primary target level for SBP and DBP was <140 mmHg and <90 mmHg, respectively.

All patients underwent the following examinations: assessment of traditional risk factors, physical examination, clinical and biochemical laboratory methods, 12-lead ECG, echocardiography, and 24-hour ABPM. Office BP was measured using a mercury sphygmomanometer, according to Korotkov's method. BP was measured 3 times, and the means of these measurements were used in the analyses. The 24-hour ABPM was performed using a BR-102 plus (SCHILLER, Switzerland).

Echocardiography was carried out according to the recommendations of the American Society of Echocardiography in M- and B-modes using Philips EnVisor C Ultrasound Machine (the Netherlands). The following parameters were measured and calculated: IVST, PWT, LVEDD, LVESD, EF, LVEDV, and LVM (LVM was calculated using the formula R. Devereux (1994). LVM was indexed to body surface area (LVMI). Left ventricular hypertrophy (LVH) was defined as LVMI of >95 g/m^2 (for women) and >115 g/m^2 (for men).[1] The ratio of peak early filling velocity to peak atrial filling velocity (PE/PA) was calculated.

Ultrasound scans of the left and right carotid arteries were performed with a 7.5 MHz probe using a duplex B-mode scanner with a resolution of 0.1 to 0.2 mm. CIMT was

measured in the distal wall of the CCA approximately 1 cm below the beginning of the bulb.

The level of MAU was determined by the method of enzymatic analysis on the biochemical analyzer "Daytona TM" ("Rendox," Great Britain), allowing to estimate the MAU in the range of 30-300 mg/L and above.

The pulse contour analysis was carried out using the SphygmoCor device (AtCor Medical, Australia), which obtains peripheral arterial pressure waveforms by applying an arterial applanation tonometer to the wrist. Such indicators as the central SBP (SBPc), central DBP (DBPc), central PP (PPc), AA, AIx, and PWV were analyzed.

Blood levels of TC, TG, HDL-C, LDL-C, and VLDL-C were determined in the venous blood using automatic biochemical analyzer Daytona (RANDOX, United Kingdom) and RANDOX test systems by the enzymatic colorimetric method. The content of LDL-C was calculated according to Fridvald's formula.

Statistical analysis was performed using the statistical software «Statistica» (v10.0, StatSoft, USA). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean± standard deviation (SD) for continuous variables. The Mann-Whitney U Test was used to compare the differences between the two independent groups (for nonparametric data). The Wilcoxon criterion was used to compare the differences between the paired samples. Group comparisons with respect to categorical variables were performed using chi-square test. A probability value of $P<0.05$ was considered statistically significant.

The study protocol was reviewed and approved by the Ethics Committee of the Republican Specialized Centre of Cardiology. All participants provided the written informed consent.

Results

The average age of the patients was 53.1±11.2 years, the average duration of AH was 8.5±7.2 years. Before the start of therapy, the average SBP in the groups was 156.2±16.6 mmHg, DBP – 90.9±11.2 mmHg (Table 1). Obesity (BMI≥30 kg/m^2) was found in 53(52.5%) patients, and 38(37.6%) patients were overweight. LVH, according to the 2018 ESC/ESH criteria, was detected in 79.2% of patients. Dyslipidemia was detected in 73.3% of cases, IMT thickening in 66.3% of cases, and an increased AS in 47.5% of patients. Thus, according to the risk stratification of patients with AH, more than half had high and very high cardiovascular risk.

Analysis of the office BP indicators showed high antihypertensive efficacy of 6-month therapy in both groups, regardless of the therapy regimens (Table 2). In Group 1, SBP, DBP, and BPmean decreased from 153.0±14.7 mmHg to 120.3±8.5 mmHg (P<0.001), from 90.2±11.4 mmHg to 77.7±5.8 mmHg (P<0.001), and from 111.1±11.6 mmHg to 91.9±6.1 mmHg (P<0.001), respectively. In Group 2, SBP, DBP, and BPmean decreased from 159.3±17.9 mmHg to 122.9±7.6 mmHg (P<0.001), from 91.5±11.1 mmHg to 78.5±4.3 mmHg (P<0.001), and from 114.1±11.6 mmHg to 93.3±4.6 mmHg (P<0.001), respectively. In general, a significant positive dynamics in indicators of the DBPP was found in both groups. In particular, average 24-h SBP and DBP, average daytime SBP and DBP, average nighttime SBP and DBP, daytime and nighttime variability in SBP and DBP, as well as daytime and nighttime elevated SBP and DBP load indices significantly decreased after 6 months of therapy in both groups (Table 3).

Table 1.

Clinical characteristics of AH patients in the study groups

Parameters	General group	Group 1 (Az+Ind)	Group 2 (Az+Nit)	*P*-value
Age, yrs	53.1±11.2	50.9±10.6	55.3±11.5	0.058
AH duration, yrs	8.5±7.2	7.2±6.3	9.8±7.8	0.273
SBP, mmHg	156.2±16.6	153±14.7	159.3±17.9	0.485
DBP, mmHg	90.9±11.2	90.2±11.4	91.5±11.1	0.749
BPmean, mmHg	112.6±11.6	111.1±11.6	114.1±11.6	0.613
BMI, kg/m^2	30.7±4.6	30.7±3.8	30.6±5.3	0.921
BMI >30 kg/m^2, %	53 (52.5%)	28 (56.0%)	25 (49.0%)	0.482
BMI >25<30 kg/m^2, %	38 (37.6%)	19 (38.0%)	19 (37.2%)	0.938
LVH, %	80 (79.2%)	38 (76.0%)	42 (82.3%)	0.431
PE/PA< 1.0, %	75 (74.3%)	33 (66.0%)	42 (82.3%)	0.060
PWV >10 m/sec, %	48 (47.5%)	22 (44.0%)	26 (51.0%)	0.482
CIMT ≥0.9 mm, %	67 (66.3%)	28 (56.0%)	39 (76.5%)	0.029
Dyslipidemia, %	74 (73.3%)	36 (72.0%)	38 (74.5%)	0.776

P-value - between Groups 1 and 2.

Achieving the target level of BP in both groups provided high organ-protective efficacy, expressed in a significant regression of LVH and LV dimensions, a decrease in the CIMT and arterial rigidity. However, the best cardio- and vaso-protective efficacy was noted in Group 1. The regression of LVH was assessed by the dynamics of LVMI (Table 4). In particular, in Groups 1 and 2, LVMI decreased from 127.4±32.9 g/m^2 to 110.3±29.0 g/m^2 (P<0.001) and from 138.7±31.9 g/m^2 to 116.6±30.3 g/m^2 (P<0.001), respectively. At the same time, the degree of decrease in LVMI was -13.3±15.6% in Group 1, and -14.4±17.9% in Group 2. A significant regression of LVH against the background of 6-month dual therapy in both groups was accompanied by an improvement in LVDF. In Group 1, PE/PA after treatment was 1.10±0.30 versus 0.90±0.30 (P<0.001) before treatment, in Group 2 – 1.00±0.30 versus 0.90±0.20 (P<0.001), having reached the standard values. However, LAV and LAVI significantly decreased (from 50.7±11.6 mL to 45.1±9.0 mL (P<0.02) and from 25.3±5.4 mL/m^2 to 23.2±3.8 mL/m^2 (P<0.02), respectively) only in Group 1. A significant decrease in LVMM in both groups was associated with a decrease in the degree of concentric LVH. We found a significant increase in the LVEDV/LVMM index: from 0.51±0.07 mL/g to 0.57±0.14 mL/g (P<0.001) in Group 1 and 0.50±0.11 mL/g to 0.54±0.12 mL/g (P<0.02) in Group 2. Both dual-therapy regimens were characterized by a significant increase in LVEF.

Table 2.
Antihypertensive efficacy of 6-month therapy in the study groups

Parameters		General group	Group 1 (Az+Ind)	Group 2 (Az+Nit)	Mann-Whitney U Test		
					U	Z	P-value
SBP, mmHg		156.2±16.6 / 121.6±8.1*	153±14.7 / 120.3±8.5*	159.3±17.9 / 122.9±7.6*	1055	1.523	0.128
					1003	2.175	0.030
DBP, mmHg		90.9±11.2 / 78.1±5.1*	90.2±11.4 / 77.7±5.8*	91.5±11.1 / 78.5±4.3*	1182	0.669	0.504
					1188	0.741	0.459
BPmean, mmHg		112.6±11.6 / 92.6±5.4*	111.1±11.6 / 91.9±6.1*	114.1±11.6 / 93.3±4.6*	1088	1.272	0.203
					1007	1.958	0.050
Δ% SBP		-21.5±7.8	-20.8±8.5	-22.2±7.0	1208	-0.456	0.648
Δ% DBP		-13.0±9.9	-12.9±9.6	-13.2±10.3	1235	-0.273	0.785
Δ% BPmean		-17.2±7.5	-16.7±7.8	-17.7±7.1	1217	0.394	0.693
					χ^2	*P*-value	
Achieving the target level of BP	SBP	95 (94.1%)	48 (96.0%)	47 (92.2%)	0.67	0.414	
	DBP	97 (96.0%)	47 (94.0%)	50 (98.0%)	1.08	0.298	
	BPmean	100 (99.0%)	49 (98.0%)	51 (100.0%)	1.03	0.310	

The numerator represents the results before treatment and the denominator - after treatment. P-value - between Groups 1 and 2.
** - P<0.001- before treatment and after 6-month therapy within the group.*

Table 3.
Dynamics of ABPM indicators against the background of 6-month dual therapy in the study groups

Parameters	General group	Group 1 (Az+Ind)	Group 2 (Az+Nit)	Mann-Whitney U Test		
				U	Z	*P*-value
Average 24-h SBP, mmHg	141.3±15.3 / 121.1±11.3*	140.2±15.7 / 118.5±12.7*	142.6±15 / 123.7±9.1*	655	1.032	0.302
				520	2.401	0.016
Average 24-h DBP, mmHg	86.6±11.7 / 73.4±8.7*	87.6±13.1 / 73.1±9.4*	85.5±10.0 / 73.7±8.0*	702	-0.561	0.575
				722.5	0.560	0.576
Average daytime SBP, mmHg	142.8±16.2 / 122.4±11.5*	141.4±16.7 / 120.1±13.3*	144.3±15.6 / 124.8±8.8*	655	1.212	0.225
				552	2.233	0.026
Average daytime DBP, mmHg	88.3±12.5 / 75.3±9.1*	89.3±14.3 / 75.2±10.0*	87.2±10.3 / 75.5±8.1*	739	-0.388	0.698
				728	0.506	0.613
Average nighttime SBP, mmHg	135.6±15.4 / 117.6±12.7*	133.1±16.0 / 113.9±12.4*	138.4±14.5 / 121.5±12.1*	553.5	1.897	0.058
				483	2.910	0.004
Average nighttime DBP, mmHg	81.5±11.9 / 68.6±9.8*	82.2±12.5 / 67.8±9.2*	80.8±11.3 / 69.4±10.3*	708	-0.321	0.748
				676	1.016	0.309
24- h SBP variability, mmHg	16.4±4.3 / 12.3±2.8*	16.2±4.9 / 11.8±2.5*	16.7±3.5 / 12.9±3.0*	635	1.231	0.218
				598.5	1.776	0.076
24- h DBP variability, mmHg	14.2±4.1 / 11.4±3.0*	14.1±4.6 / 11.0±2.8*	14.4±3.6 / 11.8±3.1*	724	0.340	0.734
				656	1.211	0.226
Daytime SBP variability, mmHg	16.1±4.7 / 12.0±2.9*	15.9±5.2 / 11.4±2.2*	16.3±4.2 / 12.7±3.4*	706	0.711	0.477
				614.5	1.618	0.106
Daytime DBP variability, mmHg	14.5±5.0 / 11.0±3.0*	14.4±5.3 / 10.4±2.5*	14.7±4.7 / 11.5±3.4°	742	0.358	0.720
				644	1.329	0.184
Nighttime SBP variability, mmHg	14.3±5.1 / 10.7±3.6*	13.8±5.4 / 10.6±3.7°	14.9±4.8 / 10.9±3.5*	602	1.223	0.221
				729	0.495	0.620
NighttimeDBP variability, mmHg	10.9±4.1 / 9.0±3.7°	10.4±4.5 / 8.6±4.3	11.3±3.6 / 9.5±3.1°	616.5	1.072	0.284
				629.5	1.471	0.141
Daytime SBP load, %	48.9±29.9 / 14.2±20.1*	44.8±30.3 / 12.9±22.1*	53.2±29.1 / 15.6±17.9*	614	1.455	0.146
				597	1.847	0.065
Daytime DBP load, %	43.2±28.4 / 12.3±17.4*	45.0±29.0 / 12.1±19.1*	41.4±28.0 / 12.6±15.8*	613.5	-0.574	0.566
				727	0.528	0.597
Nighttime SBP load	74.3±27.0 / 41.1±33.1*	67.7±28.6 / 28.1±30.4*	81.5±23.4 / 54.4±30.5*	539.5	2.086	0.037
				429.5	3.457	0.001
Nighttime DBP load, %	52.9±32.7 / 17.9±26.1*	52.0±35.1 / 14.0±23.2*	53.8±30.3 / 21.9±28.5*	604.5	0.255	0.799
				607.5	1.819	0.069
Nocturnal SBP fall,%	4.8±7.4 / 3.5±6.6	5.5±7.6 / 4.4±5.7	4.0±7.2 / 2.6±7.4	640.5	-0.823	0.410
				645	-1.321	0,186
Nocturnal DBP fall,%	7.5±10.2 / 8.2±8.7	8.2±11.0 / 8.4±7.5	6.8±9.3 / 7.9±9.8	612.5	-0.753	0.451
				743	-0.358	0.720

The numerator represents the results before treatment and the denominator - after treatment. P-value - between Groups 1 and 2.
** - P<0.001 and ° - P<0.02 before treatment and after 6-month therapy within the group.*

In both groups, we found a decrease in the CIMT and MAU level (Table 4). However, the left CIMT significantly decreased and reached the standard values only in Group 1: from 0.90±0.20 mm to 0.86±0.11 mm (P<0.02).

The effectiveness of both dual-therapy regimens, with the Az+Ind having some advantage, was found for the parameters of central hemodynamics and AS (Table 5). In particular, the indicators of SBPc, DAPc, PPc, and AA significantly improved, and the PWV decreased. However, the AI significantly decreased only in Group 1.

Both dual-therapy regimens had a positive effect on the dynamics of biochemical parameters (Table 6). LDL-C decreased from 124.5±29.2 mg/dL to 105.5±28.6 mg/dL (P<0.001) in Group 1, and from 129.7±48.7 mg/dL to 103.9±32.7 mg/dL (P<0.001) in Group 2. A significant decrease in the levels of TG and FBG was observed in Group 1: from 175.4±88.2 mg/dL to 146.5±52.3 mg/dL (P<0.02) and from 5.7±1.0 mmol/L to 5.4±0.6 mmol/L (P<0.02), respectively. In addition, there was a significant decrease in the blood levels of creatinine and uric acid and an increase in GFR.

Thus, both dual-therapy regimens had a positive effect on the metabolic profile, with the Az+Ind therapy having some advantages.

It is well known that AHMs must not only have a prolonged antihypertensive effect during the day, but also contribute to the improvement of DBPP. It is very important to ensure an organ-protective effect during treatment. All modern AHM classes have approximately the same antihypertensive efficacy, but not all have the same anti-remodeling effect in AH patients. Among AHMs, ARBs have a fairly convincing evidence base in improving the prognosis of AH patients.[12-18] A unique feature of azilsartan is its ability to significantly improve DBPP, in comparison with other ARBs, which undoubtedly affects the prognosis of AH patients.[8-11] In particular, by reducing the average 24-h SBP and DBP, BP variability, and normalizing the degree of nocturnal BP reduction, azilsartan helps to reduce the degree of target organ damage and the risk of developing cardiovascular complications in AH patients. CCBs also have a fairly convincing evidence base in improving the prognosis of AH patients (ASCOT, TOMHS, PREVENT, ALLHAT).

Table 4.

Dynamics of markers of cardiovascular remodeling against the background of 6-month dual therapy in the study groups

Parameters	General group	Group 1 (Az+Ind)	Group 2 (Az+Nit)	Mann-Whitney U Test		
				U	Z	*P*-value
IVST, cm	1.17±0.14 1.08±0.17*	1.15±0.14 1.07±0.16*	1.19±0.14 1.09±0.18*	1081.5	1.313	0.189
				1084	1.300	0.194
PWT, cm	1.02±0.17 0.97±0.15*	1.00±0.15 0.94±0.14°	1.04±0.19 1.00±0.16*	1064	1.432	0.152
				1054	1.506	0.132
LVEDV/LVM, mL/mg	0.51±0.09 0.55±0.13*	0.51±0.07 0.57±0.14*	0.50±0.11 0.54±0.12°	1079.5	-1.325	0.185
				1093.5	-1.229	0.219
LVEDD, cm	5.1±0.5 4.9±0.5*	5.1±0.5 4.9±0.5*	5.2±0.5 4.9±0.5*	1056.5	1.486	0.137
				1184	0.616	0.538
LVESD, cm	3.3±0.4 3.2±0.4^	3.3±0.4 3.2±0.4	3.3±0.3 3.3±0.4	1130.5	0.983	0.326
				1198.5	0.353	0.724
EF, %	65.3±4.3 76.4±4.4*	65.1±4.4 76.6±4.2*	65.4±4.2 76.2±4.5*	1212.5	0.421	0.674
				1181.5	-0.131	0.895
PE/PA	0.90±0.30 1.10±0.30*	0.90±0.30 1.10±0.30*	0.90±0.20 1.00±0.30*	1233	-0.282	0.778
				1173	-0.689	0.491
E/e’	0.07±0.02 0.08±0.02	0.08±0.02 0.08±0.03	0.07±0.02 0.08±0.02	841.5	-1.372	0.170
				992.5	-1.005	0.315
LAV, mL	49.8±11.2 46.2±9.0°	50.7±11.6 45.1±9.0°	48.9±10.9 47.6±9.1	533.5	-0.733	0.464
				216	1.153	0.249
LAVI, mL/m^2	25.3±5.6 23.8±4.3*	25.3±5.4 23.2±3.8°	25.3±6.0 24.7±4.8	576	-0.222	0.824
				230	0.850	0.395
LVM, g	259.6±67.7 219.7±62.2*	248.8±67.8 213.8±62.6*	270.2±66.7 225.3±61.9*	1048.5	1.535	0.125
				1124.5	0.858	0.391
LVMI, g/m^2	133.1±32.8 113.5±29.7*	127.4±32.9 110.3±29.0*	138.7±31.9 116.6±30.3*	996	1.892	0.059
				1100	0.865	0.387
CIMT (left), mm	0.93±0.15 0.9±0.16°	0.90±0.10 0.86±0.11°	1.00±0.20 0.90±0.20	927.5	2.405	0.016
				911.5	2.536	0.011
CIMT (right), mm	0.93±0.21 0.89±0.16*	0.90±0.20 0.80±0.10°	1.00±0.20 0.90±0.20^	978	2.053	0.040
				962.5	2.190	0.029
MAU, mg/L	29.9±31.7 16.5±18.1*	30.5±27.8 17.5±18.4*	29.3±34.9 15.7±17.9*	949.5	-1.112	0.266
				1018.5	-0.589	0.556
Δ% LVMI	-13.9±16.7	-13.3±15.6	-14.4±17.9	1165	-0.410	0.682
Δ% MAU	-12.9±94.1	-22.2±56.3	-5.0±116.9	1085.5	-0.080	0.936

The numerator represents the results before treatment and the denominator - after treatment. P-value - between Groups 1 and 2.
** - P<0.001; ° - P<0.02; ^ - P<0.05 before treatment and after 6-month therapy within the group.*

Table 5.
Dynamics of parameters of central hemodynamics and AS against the background of 6-month dual therapy in the study groups

Parameters	General group	Group 1 (Az+Ind)	Group 2 (Az+Nit)	Mann-Whitney U Test		
				U	Z	*P*-value
SBPc, mmHg	156.9±22.8 126.4±15.8*	154.4±21.1 126.5±21.2*	159.5±24.3 126.3±8.0*	1058	1.321	0.187
				992.5	1.773	0.076
DBPc, mmHg	89.6±14.1 77.7±11.0*	90.8±14.8 77.9±14.2*	88.4±13.3 77.5±6.7*	1170	-0.552	0.581
				1070.5	1.450	0.147
PPc, mmHg	67.4±17.0 49.6±11.2*	64.1±15.5 50.3±13.6*	70.7±18.0 48.9±8.5*	1011.5	1.787	0.074
				1239.5	0.238	0.812
AA, mmHg	15.0±8.7 11.1±7.9*	13.9±8.3 10.2±8.6°	16.1±9.0 12.0±7.0°	1171	0.704	0.482
				961.5	2.131	0.033
AI, %	30.4±11.3 27.5±13.7	29.5±11.6 24.8±13.2^	31.4±10.9 30.1±13.8	1192.5	0.557	0.577
				922	2.256	0.024
PWV, m/sec	10.1±3.2 7.4±2.0*	9.6±3.1 7.4±2.3*	10.5±3.2 7.4±1.7*	1051.5	1.515	0.130
				1208.5	0.449	0.654

The numerator represents the results before treatment and the denominator - after treatment. P-value - between Groups 1 and 2.
** - P<0.001; ° - P<0.02; ^ - P<0.05 - before treatment and after 6-month therapy within the group.*

Table 6.
Dynamics of biochemical parameters against the background of 6-month dual therapy in the study groups

Parameters	General group	Group 1 (Az+Ind)	Group 2 (Az+Nit)	Mann-Whitney U Test		
				U	Z	*P*-value
FBG, mmol/L	5.6±0.8 5.4±0.6°	5.7±1.0 5.4±0.6°	5.6±0.6 5.5±0.6	1261.5	-0.089	0.929
				1124.5	0.862	0.388
Creatinine, μmol/L	83.7±20.4 78.5±16.5*	83.0±18.8 77.9±14.6°	84.3±21.9 79.1±18.2^	1270	-0.031	0.976
				1228.5	0.141	0.888
GFR, mL/min/1.73 м^2	83.9±18.6 89.6±16.0*	84.5±16.4 91.0±14.5*	83.4±20.7 88.2±17.4^	1257	0.119	0.905
				1113.5	-0.935	0.350
Uric acid, mg/dL	6.2±1.8 5.4±1.4*	6.1±1.6 5.3±1.5*	6.3±1.9 5.5±1.3*	1195	0.540	0.589
				1091.5	0.931	0.352
TC, mg/dL	210.6±47.5 184.4±33.1*	205.5±36.3 184.1±27.6*	215.7±56.3 184.6±37.9*	1184.5	0.611	0.541
				1247.5	-0.010	0.992
TG, mg/dL	173.5±96.7 147.8±51.8°	175.4±88.2 146.5±52.3°	171.6±105.2 149.0±51.7	1175.5	-0.673	0.501
				1244	0.034	0.972
LDL-C, mg/dL	127.2±40.1 104.7±30.6*	124.5±29.2 105.5±28.6*	129.7±48.7 103.9±32.7*	1033.5	1.638	0.101
				1135	0.787	0.431
HDL-C, mg/dL,	48.1±12.5 49.0±10.8	46.8±13.4 48.1±10.7	49.5±11.5 49.8±11.0	1220	0.370	0.711
				1157.5	-0.631	0.528
Atherogenic index	3.5±1.0 3.1±0.9*	3.7±0.9 3.1±0.9*	3.4±1.0 3.0±0.8^	1033.5	-1.491	0.136
				1108.5	-0.982	0.326

The numerator represents the results before treatment and the denominator - after treatment. P-value - between Groups 1 and 2.
** - P<0.001; ° - P<0.02; ^ - P<0.05 - before treatment and after 6-month therapy within the group.*

At the same time, not all AHM classes are able to improve cognitive functions in AH patients. A unique feature of CCBs is their ability to penetrate the blood-brain barrier and reduce the metabolism of monoamine mediators, the deficiency of which occurs in degenerative dementia. This property underlies their preventive action against cognitive impairment in AH patients. Among CCBs, nitrendipine has a strong evidence base.[19] The effect of nitrendipine on the prevention of cardiovascular complications in patients over age 60 with ISAH, as well as changes in quality of life and the incidence of post-stroke dementia, were assessed in the randomized, double-blind, placebo-controlled, multicentre Syst-Europe trial.[20] There was a reduction in cardiovascular mortality by 27%, in myocardial infarction by 56%, in stroke by 42%, and in the combined rate of all fatal and non-fatal cardiovascular endpoints by 31%. At the same time, nitrendipine had a pronounced cerebroprotective effect, reducing the risk of developing dementia by 55%. In the Syst-China study,[21] a nitrendipine-based regimen resulted in a significant reduction in the risk of stroke by 38%, all-cause mortality by 39%, cardiovascular mortality by 39%, death rates from stroke by 58%, and all cardiovascular events by 37%. In addition, there was an improvement in glomerular filtration by 13%, as well as in cerebral hemodynamics and cognitive function by 8%, demonstrating nitrendipine-based neuroprotective and nephroprotective effects.[22] Indapamide, a long-studied diuretic that lowers blood pressure mainly due to a specific vascular effect and has metabolic neutrality, also has a fairly convincing evidence base (LIVE, PATS, VASK, TOMHS, SHEP) for its effectiveness.

Our clinical experience of the combined use of Az+Ind and As+Nit showed high antihypertensive efficacy, especially in relation to DBPP, regardless of the dual-therapy regimens. In particular, average 24-h SBP and DBP, average daytime SBP and DBP, average nighttime SBP and DBP, daytime and nighttime variability in SBP and DBP, as well as daytime and nighttime elevated SBP and DBP load indices significantly decreased after 6 months of therapy in both groups

Improvement in the DBPP was accompanied by significant organ protection, especially against the background of Az+Ind; in particular, we found a more pronounced improvement in LVDF. Combined therapy with Az+Ind and Az+Nit was accompanied by a decrease in IMT. At the same time, a positive trend in all indicators of central hemodynamics and AS was found against the background of Az+Ind.

Thus, both dual-therapy regimens showed high antihypertensive efficacy with an improvement in DBPP, and a positive effect on the metabolic profile, nephroprotection, and good tolerability. However, only the Az+Ind therapy led to an improvement in LVDF and a decrease in all AS parameters and the levels of FBG and TG.

Conclusions

1. The 6-month dual therapy with Az+Ind and Az+Nit is characterized by high antihypertensive efficacy with a significant positive effect on the DBPP parameters in AH patients.

2. Achieving the target level of BP in AH patients provides better organ-protective efficacy against the background of the therapy with Az+Ind than with Az+Nit, which is expressed in a more pronounced improvement in the LVDF (decreasing LAV and LAVI), a decrease in the CCA-IMT on both sides, and a significant improvement in the parameters of central hemodynamics and AS.

3. Dual therapy with Az+Ind and Az+Nit in AH patients is accompanied by a positive effect on the metabolic profile and excellent nephroprotection, with an advantage in the Az+Ind group. A significant decrease in the blood level of LDL-C, TC, and uric acid is characteristic in both groups of patients. A significant decrease in the levels of FBG and TG occurs only in the Az+Ind therapy.

Competing Interests

The authors declare that they have no competing interests.

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***Corresponding author**: Guzal Abdullaeva, PhD, ScD. Republican Specialized Center of Cardiology. Tashkent, Uzbekistan. E-mail: guzal-abdullaeva@bk.ru*

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